C-Reactive Protein and Vulnerability to Mental Stress-Induced Myocardial Ischemia

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Myocardial ischemia provoked in the laboratory during mental stress (MSI) in patients with stable coronary artery disease (CAD) predicts subsequent clinical events. The pathophysiology of MSI differs from that of exercise ischemia, and the mechanisms tying MSI to poor prognosis are not known. C-reactive protein (CRP) is a risk marker for cardiovascular events in patients with CAD, but little is known regarding the relationship of CRP to MSI. The purpose of this study was to examine the association of CRP to risk of MSI in CAD patients. Eighty-three patients with stable CAD underwent simultaneous single-photon emission computed tomography (SPECT) imaging with technetium-99m tetrofosmin myocardial perfusion imaging (MPI) and transthoracic echocardiography (TTE), at rest and during MS induced by laboratory mental stress. Serum CRP levels were measured 24 h after MS. MSI was defined by the presence of a new perfusion defect on SPECT and/or new regional wall motion abnormality on TTE during MS. Of the 83 patients, 30 (36%) developed MSI. There was no difference in gender, sex, BMI, histories of diabetes, hypertension, smoking, lipid profile, medications used (including statins, β-blockers, ACE inhibitors, and aspirin), or hemodynamic response during MS between those with and without MSI. In univariate logistic regression analysis, each unit (1 mg/L) increase in CRP level was associated with 20% higher risk of MSI (OR 1.2, 95% CI 1.01-1.39, $P = .04$). This relationship remained in multivariate models. These data suggest that levels of CRP may be a risk marker for MSI in patients with CAD.

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INTRODUCTION

Levels of chronic stress, most notably demonstrated by demands at work (1), and socioeconomic status (2–3) have been associated with increased risk of atherosclerotic disease, while acute stress, whether provoked by national emergencies (4–5) or routine experiences of moderate to extreme anger (6–9), have been associated with the triggering of acute coronary syndrome (ACS), and catastrophic left ventricular failure (10). Furthermore, research over the past 20 y has demonstrated that, in the laboratory, mental and emotional stress can provoke ischemia (MSI) in 30%-50% of patients with chronic, stable coronary disease (CAD) (11–12). The pathophysiology of MSI differs from that of exercise-induced ischemia (6,11–12), and CAD patients who evidence ischemia during mental stress are at increased risk of major adverse cardiovascular events and death (MACE) (13–16).

The way the mechanism(s) by which mental stress provoked myocardial ischemia in patients with CAD ultimately contribute(s) to increased risk for MACE have not been fully defined (17–19). Evidence suggests potential involvement of hemodynamic stress, alterations in coronary vasoreactivity, platelet activation, arrhythmogenesis, increased sympathetic activation, and endothelial injury (6,17). In addition to increases in sympathetic activity, we and others have also observed parasympathetic withdrawal in both healthy subjects and patients with CAD during laboratory MS (18,20–24). The role of sympathetic regulation of cytokine synthesis/release and inflammation has been extensively investigated in experimental models during the past 2 decades (25–28). Recently, however, the role of parasympathetic activity in the control of immunity and inflammation has been described in bench and animal models (27,29–30). It has been shown that the efferent vagus nerve inhibits the release of pro-inflammatory cytokines and regulates inflammation in real time, similar to its effects on the heart rate and gastrointestinal function (27,29–32). This function of the efferent vagus nerve has been termed the cholinergic anti-inflammatory pathway (27,29–30). Because MS causes parasympathetic withdrawal, inflammatory processes associated with dysfunction of this cholinergic anti-inflammatory pathway may be 1 underlying mechanism of MSI.

The level of C-reactive protein (CRP), an indicator of chronic inflammation, has been identified as a risk marker for ACS (33). To date, the importance of inflammatory processes to the provocation of MSI has not been established. The objective of this study was to examine the association of CRP to the risk of developing MSI in patients with stable CAD. Data were drawn from an ongoing study of vascular processes in MSI.

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Table 1. Patient Characteristics Stratified by Mental Stress Ischemia (MSI)

Characteristics	MSI	No-MSI	*P*-value*
N (%)	30 (36%)	53 (54%)	
Demographics			
Age (Mean)	66.0	67.2	0.51
Sex % female	5.4%	10.0%	0.43
PMHX			
Diabetes†	32.4%	23.3%	0.33
Hypertension†	86.5%	86.7%	0.98
Smoker	13.5%	21.7%	0.32
Hyperlipidemia†	97.3%	90.0%	0.18
BMI	30.1	29.1	0.22
Lipid Panel			
Total Cholesterol	161.4	165.3	0.57
LDL	90.1	89.2	0.88
HDL	44.6	47.0	0.39
Triglycerides	149.6	143.0	0.79
Medications			
Aspirin	64.9%	68.3%	0.73
β-Blocker	70.3%	80.0%	0.28
Statins	91.9%	86.7%	0.44
ACE inhibitors	54.1%	52.3%	0.95

*Patients with and without MSI were compared by means of Chi-square tests for categorical data, t-tests for normally distributed data, and Wilcoxon rank tests for non-normal data.
†Information regarding diabetes, hypertension, and hyperlipidemia was collected by medical chart review (for example, medical note indicating the presence of risk factor and/or medication treatment for the condition)

MATERIALS AND METHODS

Patient Population

We studied 83 patients with chronic stable CAD diagnosed on the basis of a defect on stress myocardial perfusion imaging, wall motion abnormality on echocardiography, epicardial stenosis on coronary angiography, or history of documented myocardial infarction. Patients were excluded if they had a history of recent unstable angina (within 3 months), recent myocardial infarction or coronary revascularization (within 6 months), uncompensated congestive heart failure (left ventricular ejection fraction < 30%), major psychiatric disorder, history of substance abuse, or treatment with any psychotropic medications. Informed consent was obtained in accordance with the guidelines of the Human Studies Subcommittee of the VA Connecticut Healthcare System, West Haven, Connecticut, and the Human Investigations Committee of Yale University School of Medicine, New Haven, Connecticut, which approved this study. The demographic characteristics of the study population are shown in Table 1.

All patients underwent simultaneous single-photon emission computed tomography (SPECT) imaging with technetium-99m tetrofosmin myocardial perfusion imaging (MPI) and transthoracic echocardiography (TTE) in the laboratory, at rest, and during MS. Serum CRP levels were measured from blood samples drawn 24 h after MS.

Measures

SPECT protocol. The imaging procedures were identical to those used clinically, and involved a 1-day rest-stress protocol. Resting SPECT imaging was performed prior to MS, 1 h after the intravenous injection of technetium-99m tetrofosmin (Tc-99m), while MS SPECT images were acquired 30 min after intravenous Tc-99m injection. Myocardial perfusion images were analyzed in the standard fashion using previously published Wackers-Liu software package developed at Yale University (34). Two experienced nuclear cardiologists interpreted all SPECT studies by visual analysis, and each region was coded as normal, reversible or partially reversible (ischemic), or fixed.

Echocardiography. Two-dimensional TTE was performed with a phased-array sector scanner (Hewlett-Packard SONOS 5500). Parasternal long axis, short-axis and apical 2- and 4-chamber views, were acquired at rest and during MS. Segmental wall motion analysis was performed by 2 experienced echocardiographers blinded to the results of the SPECT studies. Representative cycles of rest and MS images were positioned side-by-side on a quad-screen format. The development of new regional wall motion abnormalities during MS was considered an ischemic response.

CRP assay. Blood samples were obtained from a peripheral vein into a tube containing ethylenediaminetetraacetic acid. Samples were centrifuged at 3,000*g* and serum was extracted, aliquoted, and stored at ~4°C until analysis. Plasma CRP levels were determined using nephelometry (Beckman Instruments, Fullerton, CA).

Procedures

The MS protocol has been previously reported by our laboratory (11,35). Patients reported to the Nuclear Cardiology Laboratory at 9 a.m. on the morning of testing, having been instructed to abstain from tobacco use from the morning of that day (all participants indicated compliance with this instruction). After completing informed consent, an indwelling intravenous line was established. Patients were instructed to report symptoms of angina if they occurred. Tc-99m was injected and 1 h later the resting SPECT image was acquired. Patients were then instrumented with automated blood pressure cuff and 12-lead ECG. They were then instructed to rest quietly for 15 min. An imagery protocol in which the patients are instructed to imagine themselves in a relaxing place (for example, the beach on a warm sunny day) was used to facilitate relax-

Table 2. Effect of Mental stress (MS) on Hemodynamic Parameters

	Resting			MS		
Hemodynamics	MSI	No-MSI	P-value*	MSI	No-MSI	P-value*
Mean HR	56.2	56.4	0.91	67.4	67.6	0.92
Mean SBP	134.4	134.3	0.99	159.5	163.9	0.34
Mean DBP	74.1	76.0	0.40	88.1	90.5	0.29

*Patients with and without MSI were compared by means of t-tests for normally distributed data, and Wilcoxon rank tests for non-normal data

ation. Approximately 10 min into this 15 min period, a baseline TTE was acquired. At the end of the 15 min period, a baseline blood sample was drawn. The MS procedures were implemented.

The specific mental stressor used was anger recall. Patients were instructed to recall a recent incident during which they had experienced irritation, aggravation, and/or frank anger. They were then instructed to describe this incident in detail to the study psychologist, who prompted them for details concerning aspects of the incident that provoked anger. Approximately 90 s into this 7 min task, the patients were injected with Tc-99m. The timing of injection is based on data indicating that MSI when present, develops within 1 min of MS testing and is sustained for the duration of the MS task (11,36). Also at this time, stress TTE was performed. Stress SPECT images were acquired 30 min later, and the patients were then dismissed. Monitoring during the stress portion of the MPI was identical to that used for clinical (for example, exercise or pharmacologic) stress testing. In brief, heart rate, blood pressure, and 12-lead electrocardiogram were obtained at 1 min intervals. The indications for early termination of stress were also identical to those of clinical stress testing: severe angina, ST-segment depression of greater than 3 mm, any decrease in systolic blood pressure, or any significant arrhythmia.

Approximately 24 h after completion of the mental stress protocol, the patients reported to the Nuclear Cardiology Laboratory. A blood sample was obtained from each patient, from which levels of CRP were ascertained for the study reported here.

RESULTS

MSI was defined by the presence of a new myocardial perfusion defect on SPECT and/or new regional wall motion abnormality on TTE during MS. Of the 83 patients, 30 (36%) developed MSI during MS. Those with and without MSI were compared on age, gender, BMI, histories of diabetes, hypertension, smoking, medications used (including statins, β-blockers, ACE inhibitors, and aspirin), and hemodynamic response during MS, with no significant differences found (see Tables 1 and 2).

The distribution of CRP for the study population, and for those patients with and without MSI is provided in Table 3. For the study population, mean CRP was 3.04 (± 3.0); for those with MSI mean CRP was 3.99 (± 4.2) while for those without MSI mean CRP was 2.54 (± 1.9). To determine the relationship of 24 h CRP to MSI, logistic regression analysis was performed, with MSI as the dependent variable. In a univariate model, each unit (1 mg/L) increase in CRP level was associated with 20% higher risk of MSI (OR 1.2, 95% CI 1.01-1.39; $P = 0.04$). In models adjusted for LDL (OR 1.2, 95% CI 1.00-1.39; $P = 0.05$), and for the standard risk factors of age, gender, diabetes, hypertension, hyperlipidemia, smoking, BMI, and for ACE inhibitor, β-blocker, and aspirin medications, (OR 1.2, 95% CI 1.01-1.46, $P = 0.04$) the relationship of CRP to MSI remained significant.

To ascertain whether thresholds of increased MSI risk conformed to thresholds of ACS risk associated with CRP, we examined the distribution of CRP level in the patient sample by tertile, with the upper tertile representing the approximate risk threshold for CRP used in clinical settings. MSI occurred in 29.6% of patients in the lower tertile CRP (≤ 1.45 mg/L), in 35.7% of patients in the intermediate tertile (1.46 to 2.98 mg/L), and in 42.7% of patients in the upper tertile (≥ 2.99 mg/L) (see Figure 1). Using one-sided Cochran-Armitage test, this increasing risk for MSI across tertiles of CRP demonstrated a non-significant trend.

Prior studies have found levels of CRP to be stable over time and not responsive to either acute stress or ischemia (37–39). As proof of principle to determine whether CRP levels 24 h after MS were comparable to CRP levels during baseline, we assayed baseline blood samples for CRP from a random sample of 12 patients (5 with MSI) and compared it to 24 h levels, finding no differences ($P = 0.73$). The mean (3.29 mg/L) and median (2.39 mg/L) CRP levels at baseline were similar to mean (3.18 mg/L) and median (2.30 mg/L) CRP levels at 24 h.

Table 3. Distribution of CRP

	Mean (SD)	Median	25th Percentile	75th Percentile	IQR
Overall	3.04 (3.00)	2.15	1.20	3.66	2.47
MSI	3.99 (4.20)	2.22	1.46	5.11	3.65
No-MSI	2.54 (1.90)	2.11	1.14	3.29	2.15

DISCUSSION

This is the 1st published report of an association among patients with CAD between level of CRP and the provocation of MSI in the laboratory. Our data showed that with each unit increase in CRP level there was a statistically significant, 20% increased risk of MSI. Furthermore, while not statistically significant, those with 24 h CRP at or above 3.0 were 30% more likely to become ischemic during mental stress than those with CRP

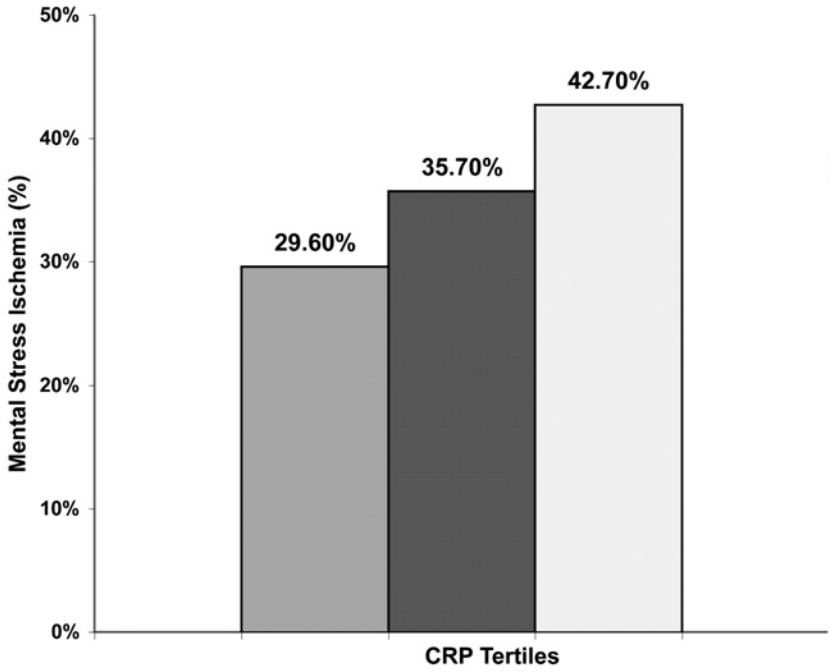

Figure 1. MSI by CRP tertiles. MSI occurred in 29.6% of patients in the lower tertile CRP (≤1.45 mg/L), in 35.7% of patients in the intermediate tertile (1.46 to 2.98 mg/L), and in 42.7% of patients in the upper tertile (≥2.99 mg/L)

below 3.0. This effect was not mitigated by the use of β-blockers or statin medications as has previously been reported for the association of CRP with induction of ischemia by exercise (37), and therefore provides further evidence that the pathophysiology of MSI is likely distinct from that of exercise-induced ischemia (6, 11–12). More importantly, the current findings suggest that underlying inflammatory processes may increase susceptibility to ischemia during episodes of mental or emotional stress for patients with chronic CAD in a process that is not influenced by standard pharmacotherapy for these patients.

The participation of inflammatory cells and mediators in atherogenesis and plaque rupture is well established (40–43). Atherosclerosis is a multifactorial, multistep disease that involves chronic inflammation at every stage, from initiation to progression and, eventually, plaque rupture. In atherosclerosis, the normal homeostatic functions of the endothelium are altered, promoting an inflammatory cascade (40–43). In this inflammatory cascade, inflammatory mediators enhance uptake by the endothelium of modified lipoprotein particles and subsequent formation of lipid-filled macrophages (40–43). This is followed by T cells entering the intima and secreting cytokines, which subsequently amplify the inflammatory response and promote the migration and proliferation of intimal smooth muscle cells, thereby promoting the growth of atherosclerotic plaque (40–43). Finally inflammatory proteins can weaken the protective fibrous cap of the atheroma, thereby increasing the risk of thrombosis and the occurrence of ACS such as unstable angina and MI (40–43).

Based on the evidence supporting a role for inflammation in the pathogenesis of atherosclerosis, protein markers of inflammation have been studied as noninvasive indicators of underlying atherosclerosis in apparently healthy individuals and of the risk of recurrent events in patients with established atherosclerotic disease (41–44). One of these markers, CRP, has proven remarkably robust as a marker of cardiovascular risk for which standardized high-sensitivity assays (hs-CRP) are widely available (41–45). Although serum CRP may be a nonspecific marker of the acute phase response to inflammation, several studies have shown that CRP is a direct participant in the progression of atherosclerosis (46–47). Furthermore, in 1 study similar to that reported here, high levels of CRP were associated with increased risk for inducible ischemia on *exercise* stress testing in patients with known CAD, though in contrast to the current study, that study found no relationship between CRP and exercise-induced ischemia among patients taking β-blockers and/or statin medications (37).

Psychosocial factors, including stress and negative emotional states, can adversely affect inflammatory processes, and increase levels of proinflammatory cytokines (39,48–50). Given the involvement of these processes in CAD progression and plaque rupture, increased levels of inflammatory markers may be 1 way that psychosocial factors contribute to triggering of ACS and sudden death (7,51). Similarly this process may in part underlie the well-established relationship between depression and reduced event-free survival in patients after ACS (52–53), as depression is associated with increased CRP level (54–55) and antidepressant therapy in depressed patients decreases CRP level (56). More research is needed regarding the role of inflammation in the pathophysiology of ischemic syndromes provoked by mental and emotional stress in patients with CAD.

The mechanisms governing the immune system and cytokine release are complex (57). The innate immune system is activated by infection and injury to release pro-inflammatory cytokines. The magnitude of the cytokine response is critical, because a deficient response may result in secondary infections, while an excessive response may be more injurious than the original insult (57). It is well known that these responses are regulated via anti-inflammatory processes, including glucocorticoids and counter-regulatory

cytokines (57). Recent research also has revealed that inflammation is tightly controlled by the autonomic nervous system, which plays an important role in the bidirectional communication between the brain and the immune system, and underlies the ability of the brain to monitor immune status and modulate inflammation (29–30,32). During inflammation, afferent vagus nerve fibers rapidly transmit immune signals to the brain, while efferent fibers inhibit the release of pro-inflammatory cytokines such as TNF-alpha, with acetylcholine acting on the α-7 receptor on macrophages (29–30,32). MS has been shown to provoke parasympathetic withdrawal (18,20–24). Therefore MSI could be due in part to modulation of this inflammatory reflex.

Furthermore, because stress provokes parasympathetic withdrawal, the cholinergic-inflammation pathway may be implicated in stress-triggered ACS. For example, pro-inflammatory cytokines IL-1 and IL-6 are released by circulating mononuclear cells, and the magnitude and duration of the stimulus provided by acute stress may be adequate to increases their levels (39). Parasympathetic withdrawal during naturalistic stress may shift the balance between anti-inflammatory and pro-inflammatory cytokines, and, in patients with elevated concentrations of CRP who are known to have a greater degree of atherosclerotic burden and increased plaque inflammation, provoke plague rapture.

Although this is the 1st study to report an association between CRP and MSI in patients with CAD, there are limitations that warrant discussion. We cannot exclude the possibility that CRP levels seen 24 h after the laboratory MS may have been a function of the MS manipulation or invoked ischemia, rather than reflecting overall baseline levels. For example, in 1 study of healthy individuals, an increase in CRP was observed after completion of 2 laboratory mental stress tasks (58). Previous studies with CAD patients however, demonstrate that neither mental stress in the lab nor transient ischemia in the naturalistic setting alters CRP levels, and that CRP levels are stable over periods of days (37–38). For example, Liuzzo and colleagues followed 48 patients with unstable angina and 20 patients with active variant angina in the coronary care unit for 48 h with continuous Holter monitoring (38). Blood samples drawn upon admission and 24, 48, 72, and 96 h later and assayed for CRP. During the 24 h of Holter monitoring, 29 of 48 (60%) with unstable angina and 18 of 20 (90%) patients with variant angina had at least 1 ischemic episode. There were however, no significant correlations between CRP values at 24, 48, and 72 h and the occurrence of ischemia, the number of ischemic episodes, the total ischemic burden, or the duration of the longest ischemic episodes during the 1st 24 hours. During the 96 h of study, the plasma concentration of CRP did not change even in patients with ischemic episodes lasting greater than 10 min. They concluded that relatively short episodes of ischemia-reperfusion, such as those commonly observed in patients with unstable angina and variant angina, do not themselves stimulate a significant increase in CRP levels. Similarly, Steptoe et al found no acute change in levels of CRP in response to laboratory MS (39). Furthermore, to establish proof of principle, we measured CRP in 12 of our subjects immediately prior to MS (5 with MSI and 7 without MSI) and found no difference between these levels and 24 h post-MS levels of CRP. While the evidence to date would suggest that CRP is a stable marker and that levels observed in CAD patients are not responsive to transient conditions or laboratory probes, the findings reported here must be interpreted with caution pending replication with additional patient samples.

Should these findings persist in experimental replication, they will have important clinical implications, suggesting that levels of CRP are associated with an increased risk of MSI in patients with CAD, and that, as CRP levels increase, the risk of MSI may increase in an incremental fashion, working through a pathophysiological pathway not influenced by standard pharmacotherapy for CAD. Therefore these data may have implications for the identification of patients who are at most risk for MSI. Further studies with larger patient population needed to verify this finding.

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